

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BRUCE D. GRANT
BIOTECHNOLOGY LAW GROUP
527 N. HIGHWAY 101, SUITE E
SOLANA BEACH, CA 92075-1173

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year)	
Applicant's or agent's file reference	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US06/30256	International filing date (day/month/year) 02 August 2006 (02.08.2006)
Applicant SEQUENOM, INC	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer

Ram Shukla

Telephone No. (571)272-0500

PATENT COOPERATION TREATY

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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year) **14 AUG 2008**

Applicant's or agent's file reference

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US06/30256

International filing date
(day/month/year) 02 August 2006 (02.08.2006)

Applicant
SEQUENOM, INC

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

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When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

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The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

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See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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Authorized officer
Ravi Shukla

Telephone No. (571)272-0500

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/US06/30256	International filing date (<i>day/month/year</i>) 02 August 2006 (02.08.2006)	(Earliest) Priority Date (<i>day/month/year</i>) 02 August 2005 (02.08.2005)
Applicant SEQUENOM, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

I. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of:

☒

the international application in the language in which it was filed.

☐

a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23 I(b))

b. ☐

This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 Rule 43.6 *bis(a)*

c. ☐

With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐

Certain claims were found unsearchable (See Box No. II)

3. ☒

Unity of invention is lacking (See Box No. III)

4. With regard to the title,

☒

the text is approved as submitted by the applicant.

☐

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒

the text is approved as submitted by the applicant.

☐

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐

as suggested by the applicant.

☐

as selected by this Authority, because the applicant failed to suggest a figure.

☐

as selected by this Authority, because this figure better characterizes the invention.

b. ☒

none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/30256

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1 and 2

- Remark on Protest**
- | | |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee. |
| <input type="checkbox"/> | The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation. |
| <input checked="" type="checkbox"/> | No protest accompanied the payment of additional search fees. |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/30256

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C12Q 1/68(2006.01);C12P 19/34(2006.01)

USPC: 435/6,91.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6, 91.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	BULLINGER, L. Gene Expression Profiling in Acute Myeloid Leukemia, J. Clinical Oncology. 10 September 2005, Vol. 23, No. 26, pages 6296-6305, entire document.	1-2
X	TOYOTA M. Methylation Profiling in Acute Myeloid Leukemia. Blood. 01 May 2001, Vol. 97, pages 2823-2829, entire document.	1-2

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
26 March 2008 (26.03.2008)

Date of mailing of the international search report
14 AUG 2008

Name and mailing address of the ISA/US
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Authorized officer
Serge Bausch
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/30256

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claims 1-2, method of determining AML prognosis by methylation of KIAA1447.

Group 2, claim 3-4, method of determining AML prognosis by methylation of ZD5sF10.

Group 3, claim 5-6, method of determining AML prognosis by methylation of HOXA1.

Group 4, claims 7-8, method of determining AML prognosis by methylation of PITX2.

Group 5, claims 9-10, method of determining AML prognosis by methylation of RUNX3.

Group 6, claims 11-12, method of determining AML prognosis by methylation of NFKbeta1.

Group 7, claims 13-14, method of determining AML prognosis by methylation of ACTG1.

Group 8, claims 15-16, method of determining AML prognosis by methylation of CDH1.

Group 9, claims 17-18, method of determining AML prognosis by methylation DUSP4.

Group 10, claims 19-20, method of determining AML prognosis by methylation FARP4.

The inventions listed as Groups 1-10 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack a special technical feature that joins the claimed inventions. In the instant case, the special technical feature of group 1 is methylation of KIAA1447, group 2 is methylation of ZDF5SF10, group 3 is methylation of HOXA1, group 4 is methylation of PITX2, group 5 is methylation of RUNX3, group 6 is methylation of NFKbeta1, group 7 is methylation of ACTG1, group 8 is methylation of CDH1, group 9 is methylation of DUSP4, group 10 is methylation of FARP4. The invention of group 1 does not recite the methylation of any of the genes recited in groups 2-10, the invention of group 2 does not recite the methylation of any of the genes recited in groups 1 and 3-10, etc. and therefore group 1-10 lack a single inventive concept because they lack a shared special technical feature.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
BRUCE D. GRANT
BIOTECHNOLOGY LAW GROUP
527 N. HIGHWAY 101, SUITE E
SOLANA BEACH, CA 92075-1173

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 14 AUG 2008	
FOR FURTHER ACTION See paragraph 2 below	
Applicant's or agent's file reference	
International application No. PCT/US06/30256	International filing date (day/month/year) 02 August 2006 (02.08.2006)
Priority date (day/month/year) 02 August 2005 (02.08.2005)	
International Patent Classification (IPC) or both national classification and IPC IPC: C12Q 1/68(2006.01);C12P 19/34(2006.01) USPC: 435/6,91.2	
Applicant SEQUENOM, INC	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

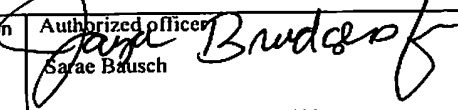
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 26 March 2008 (26.03.2008)	Authorized officer  Sarah Bausch Telephone No. (571)272-1600
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US06/30256

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US06/30256

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1 and 2

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/30256

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Claims NONE YES

Claims 1-2 NO

Inventive step (IS)

Claims NONE YES

Claims 1-2 NO

Industrial applicability (IA)

Claims 1-2 YES

Claims NONE NO

2. Citations and explanations:

Claims 1 and 2 novelty under PCT Article 33(2) as being anticipated by Toyota et al. (Blood, 2001, 97:2823-2829). Toyota et al. teach methylation profiling in acute myeloid leukemia in 15 different genes (see table 1). Therefore, Toyota et al. teach determining methylation state of a target gene and comparing the methylation state of the target Gene comprises a sequence from KIAA1447 and chromosome 17, positions 77042327-77043930. It is noted the claims do not require the sequence of KIAA1447 or the sequence from positions 77042327-77043930, the claims merely require a sequence which reads on any two or more nucleotides and therefore is anticipated by Toyota.

ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

Continuation of Detailed Reasons For Holding Lack of Unity of Invention:

Group 1, claims 1-2, method of determining AML prognosis by methylation of KIAA1447.

Group 2, claim 3-4, method of determining AML prognosis by methylation of ZDF5SF10.

Group 3, claim 5-6, method of determining AML prognosis by methylation of HOXA1.

Group 4, claims 7-8, method of determining AML prognosis by methylation of PITX2.

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Group 8, claims 15-16, method of determining AML prognosis by methylation of CDH1.

Group 9, claims 17-18, method of determining AML prognosis by methylation DUSP4.

Group 10, claims 19-20, method of determining AML prognosis by methylation FARP4.

The first named invention, which will be searched, is Group 1, claims 1-2.

The inventions listed as Groups 1-10 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack a special technical feature that joins the claimed inventions. In the instant case, the special technical feature of group 1 is methylation of KIAA1447, group 2 is methylation of ZDF5SF10, group 3 is methylation of HOXA1, group 4 is methylation of PITX2, group 5 is methylation of RUNX3, group 6 is methylation of NFKbeta1, group 7 is methylation of ACTG1, group 8 is methylation of CDH1, group 8 is methylation of CDH1, group 9 is methylation of DUSP4, group 10 is methylation of FARP4. The invention of group 1 does not recite the methylation of any of the genes recited in groups 2-10, the invention of group 2 does not recite the methylation of any of the genes recited in groups 1 and 3-10, etc. and therefore group 1-10 lack a single inventive concept because they lack a shared special technical feature.

Note: A copy of this form must be attached to the Search Report.